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NOVARTIS

Rec'd 10/29/99

October 26, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm 1061
Rockville, MD 20852

Subject: Response to Draft Guidance for Industry on ANDAs: Blend Uniformity Analysis, (Federal Register, Friday, August 27, 1999, Docket #99D-2635)

To Whom It May Concern:

Novartis Pharmaceuticals Corporation appreciates the opportunity to commend on the proposed draft has reviewed the draft guidance and has the following concerns.

Issuance of a guidance at this point is premature, as the concept of blend uniformity analysis has been incompletely studied for its robustness and scientific validity as a predictor of product quality. This point is acknowledged within the draft by the recommendation to further study blend uniformity testing within the context of the Product Quality Research Initiative and to incorporate the findings of the PQRI into the guidance. It would be logical to await the outcome of PQRI's efforts before issuing a regulatory document applicable to industry.

Some of the larger issues to be resolved by further dialog after PQRI presents its findings include:

- Effects of small sample size and methodology used to obtain representative samples on validity of data obtained and utility of routine testing
- Effects of subsequent process steps on the usefulness of blend uniformity analysis
- Appropriateness of extension of this process validation tool to routine production, across a wide subset of product presentations (solid orals to transdermals to suppositories)
- Lack of consistency to USP Content Uniformity test criteria and to ICH

Because of the need to develop knowledge in these areas, it is Novartis' recommendation that the proposed draft ANDA Guidance be held at the draft stage until the PQRI initiative is concluded and additional scientific interchange and comment have occurred.

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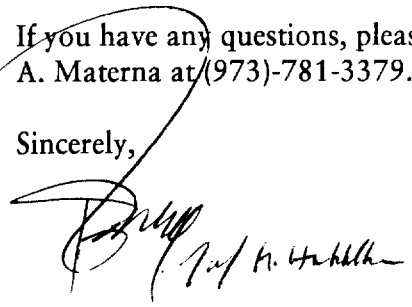
Novartis is of the opinion that no extra quality assurance will be gained by carrying out blend uniformity tests on commercial batches when the quality of the mixing process has been demonstrated during validation and when content uniformity measurements are carried out according to the USP requirements. Furthermore, significant resources and expense may be involved in routine blend uniformity testing without a corresponding increase in quality.

Thank you for the opportunity to comment. Further comments are included in tabular form in the enclosure.

If you have any questions, please contact Dr. Mathias Hukkelhoven at (973)-781-6035 or Joan A. Materna at (973)-781-3379.

Sincerely,



Dr. Mathias Hukkelhoven
Vice President, Head US DRA
US Drug Regulatory Affairs

Enclosures: Comments provided in duplicate

g/reg_int/comments/BUA FDA letter.doc

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Novartis' Comments on the Draft Guidance for Industry ANDAs: Blend Uniformity Analysis Docket No. 99B-2635

General Comments

1. The use of line numbers as done in other FDA draft guidance documents would make commenting on the draft easier and consolidation of comments clearer.

2. The general tone of this guidance draft indicates that the FDA exhibits a strong bias toward BUA testing, without providing a substantive scientific rationale for its use across the board in ANDAs, and subsequently, in NDA products ranging from solid oral dosage forms to suppositories and transdermals.

   Additionally, the position appears to be that BUA is an appropriate test for routine quality control. Other experts are equally strong that BUA is appropriate during process validation to assure blend uniformity, rather than during routine operations as a component of GMP in-process testing. Before such positions are invoked for industry, adequate research efforts through a group such as PQRI should be completed.

Lines	Comments
Page 1 footnote 2	Blend uniformity testing is proposed to be required for solid oral dosage forms, as well as applying equally to other types of blends and dosage forms. The discussion of how this testing might apply to other dosage forms such as transdermals and MDI's needs to be more fully developed to be useful.
Page 1 footnote 3	BUA should be reviewed, if applicable, within the context of ANDAs. It is not clear under what circumstances the use of BUA should be extended to NDA requirements. BUA should be reevaluated in a separate docket prior to any application to NDA products.
Page 1 I. Introduction paragraph 2	The cited rule 21 CFR 314.50(d)(1)(ii)(a) requires in process controls for drug products. Statements made in the current February 1987 FDA guidance **Submitting Documentation for the Manufacture of and Controls for Drug Products** request that analytical controls be described and that in-process specifications be supported by data that can include production and control records. These citations do not explicitly support the position that BUA "is an in-process test that is useful for ensuring the adequacy of the mixing of API's with other components of the drug product." This position is a hypothesis. Other equally scientific positions hold that BUA is more appropriately used during process validation and characterization rather than as a routine IPC. 21 CFR 211.110(a)(3) does not support the position that "adequacy of mixing ensures" uniformity and homogeneity of the end product, as mixing is but one step in the formulation process. Subsequent processing steps need to be considered. The argument is technically weak.
Page 2, paragraph 2	It would be more appropriate for the Product Quality Research Institute to establish BUA scientifically prior to issuance of the Guidance. This statement

	further supports the position that BUA's utility is an unproved hypothesis.
Page 2 II. Scope	The draft guidance references that USP Content Uniformity testing is to be conducted if drug substance is less than 50 mg. Please note that the USP does not specifically endorse or require BUA. The proposed scope creates the risk of increased regulatory burden: Proposal: BUA to be required for: • Coated tablets, other than film coated tablets • Transdermal systems • Suspensions in single-unit containers or in soft capsules • Pressurized metered-dose inhalers • Suppositories Proposal: BUA to be recommended for: • Complex dosage forms (modified release or combination products) • Capsules • Complex processes (multistep granulations) With an additional recommendation for an FDA consultation.
Page 3 paragraph 1	Reference to GMPs – does this section require BUA specifically, or require another test on **each** commercial batch to "validate the performance of processes.....variability..... "adequacy of mixing to ensure uniformity and homogeneity". - Is BUA the only test? If so, then a test as yet to be proven applicable to the dosage forms mentioned in Part II. Scope through PQRI research has been recommended by the GMP revisions as a test on each commercial batch of product. What is the basis for this FDA recommendation? - What other tests or examinations also meet this criteria? As the USP Content Uniformity test is referenced in this guidance, Novartis proposes that CU testing of finished product, in accordance with USP requirements, satisfies this FDA request and is a more appropriate, time-tested procedure. - A requirement for BUA testing conflicts with ICH Q6A recommendations that "blend uniformity testing should not be a routine, batchwise QC release test". - There is some concern that the Agency is mingling testing to "validate the performance of the process"--clearly a process validation expectation--with routine batch release of product manufactured by a validated process. Please clarify the purpose of this change in the regulatory intent of process validation.
Page 3 III. Sampling Size and Procedures	Sample sizes are specified as 1-3 times the size of the dosage form for comparison. For various reasons, it may be impossible to obtain representative samples at that small mass. Specify what the Agency would consider to be appropriate justification for larger sample size if literature references are not deemed adequate to justify this. • Define "test" batches • Thief sampling may not be representative The goal of blend sample analysis is to determine whether the blend meets the established criteria for homogeneity at that step of the process. Thus, it is critical both that the sample is representative of the whole, and that the blend analysis is relevant to the overall production process

Page 4 IV. Acceptance Criteria and Analytical Procedures	The draft guidance references USP content uniformity testing. However, the BUA proposed limits of 90-100%. RSD <5 are tighter than the USP CU limits of 85-115%, RSD <6. Please correct this discrepancy. In addition, USP CU testing allows for 2 tiers of testing, whereas the BUA does not. Therefore, the two recommendations -- one established through long USP use and one proposed to undergo concurrent PQRI investigation of its utility -- are in conflict with each other.
Attachments A & B	Please clarify the attachments, as they are unclear. • What decision is they meant to guide the sponsor to make? • If a product>50mg API and <50% API, is BUA needed? • Clarify the reason the proposed recommendation is in conflict with the USP Content Uniformity Test.

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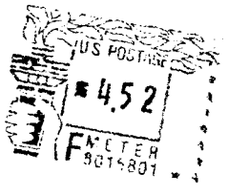

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